and growth. For example, nutrition can also influence growth indirectly by affecting behavior: abnormally high levels of amino acids in the fat body can negatively feed back on larval feeding and reduce growth (Zinke et al., 1999). The data discussed here show that low levels of fat body amino acids also reduce growth. Future research will no doubt determine whether it is intermediate amino acid levels that are needed to promote larval growth without inhibiting larval feeding. For the moment though, this paper takes us much closer to a molecular understanding the humoral control of growth in flies. It establishes the fat body as an amino acid sensor, which uses TOR signaling to generate a humoral signal that influences insulin signaling and growth in other tissues.

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Hope for a Broken Heart?

Heated debate has surrounded the issue of whether adult stem cells can differentiate into cardiac myocytes and contribute to the function of the heart. In this issue of *Cell*, Beltrami et al. (2003) demonstrate stem cells in the adult rat heart that differentiate into cardiac myocytes in vitro and, when injected into the adult rat heart, can reconstitute the injured myocardium and improve function. These findings should weigh heavily in future debates about the existence of stem cells in the adult heart and their capacity for functional repair after injury.

While newts and zebrafish can regenerate their hearts, humans (and most mammals) cannot. For this reason, myocardial infarctions produce permanent loss of cardiac muscle mass and function. One clear-cut remedy to this problem would be to stimulate the heart to make new cells by inducing the existing cardiac cells to divide. There is one mouse strain (MRL) that appears to be able to carry out some cardiac regeneration in response to injury, and much research is aimed at the genes responsible for this ability (Leferovich et al., 2001). Thus far, it appears that at least six genes contribute to this multigenic trait. There have been reports of dividing cardiac myocytes in the adult hearts of a number of mammals, but their number and physiological relevance are still debated. However, despite the existence of dividing myocytes, attempts to induce such proliferation genetically, pharmacologically, or surgically have been met with largely disappointing results. None of these stimuli has activated myocyte proliferation that is substantive enough to make a functional difference. A second potential remedy for myocardial cell loss would be to stimulate stem cells to participate in the formation of new cardiac muscle tissue. The pluripotency of embryonic stem (ES) cells is no longer a point of debate, but the restricted use of human ES cells in the United States makes them currently impractical for widespread experimentation and ultimate clinical use. Human ES cells have been shown to differentiate into cardiac myocytes when cocultured with visceral endoderm-like cells (Mummery et al., 2003). Therefore, there is still great potential for ES cells, but other options are needed.

Over the past few years, reports describing the apparent ability of bone marrow cells to populate many tissues and differentiate into host cell types (e.g., Krause et al., 2001) have generated strong interest in the potential of adult stem cells. However, substantial controversy surrounds these findings, and also the issue of whether this could occur in the heart and whether function would be affected. Experimental animal studies have provided evidence that adult stem cells can participate in the formation of new cardiac tissue, particularly in injuries. In several studies, cells were isolated from bone marrow based on cell surface antigen expression (Lin−, cKit+) and injected into the hearts of mice that had been subjected to a myocardial infarction (Jackson et al., 2001; Orlic et al., 2001a). These cells formed new cardiac tissue and functional improvement ensued. Given the invasive nature of cardiac injection, other groups subsequently showed that bone marrow-derived cells could home to an injured heart and that this process could be stimulated by growth factor treatment (stem cell factor and granulocyte-colony stimulating factor) (Orlic et al., 2001b).

Are any of these observations relevant to humans? The approach used to investigate this question was to examine hearts transplanted from human females into males for cardiac myocytes with a Y chromosome. The reasoning was that any such cell would have to be derived from a circulating stem cell or from a transdifferentiation event from a circulating cell of the transplant

recipient. Four studies were published which were heterogeneous in their findings (Glaser et al., 2002; Laflamme et al., 2002; Muller et al., 2002; Quaini et al., 2002). Two studies found ample evidence of Y chromosome-bearing cardiac myocytes in the transplanted hearts. A second study found this to be a very rare finding and questioned its significance. A third report found no evidence of Y chromosome-bearing cardiac myocytes. Multiple editorials then appeared, with much finger pointing about these discrepancies and the various parties each claiming that their own techniques were superior. The source of this exceptional furor appears to lie in the potential for medical therapy that these studies hold. The source of the cells from the various recipients remains unknown.

In addition to circulating stem cells, there has been considerable interest in the existence of resident stem cells in tissues other than the bone marrow. The article by Beltrami et al. in this issue of *Cell* provides convincing evidence that there is a stem cell population that resides in the adult heart. The stem cells can be isolated and expanded in culture indefinitely. The cells were identified and then isolated from the hearts of older adult rats (20–23 months of age). They are characterized based on the following pattern of cell surface markers: Lin−, c-Kit+, CD45−, CD34−. These cells were able to differentiate into cardiac myocytes, smooth muscle cells, and endothelial cells in culture. However, in culture, the "differentiated" cells had an immature phenotype. To test whether these cells could achieve full mature differentiation in vivo, they were injected into the myocardium of rats subjected to a myocardial infarction. These cells formed new myocardium and the hearts exhibited functional improvement. In fact, the average infarct size was greater in the treated animals than the controls, most likely because untreated animals did not survive with infarcts as large as those in the treated group. The cells were also able to form endothelial and smooth muscle structures. One potential caveat for these findings would be if the stem cells had fused with existing host cells—this might appear to be differentiation when, in fact, it would be hybrid cells giving the appearance of differentiation. However, the Beltrami et al. study ruled this out by a number of criteria, including showing that the number of new myocytes is orders of magnitude higher than the injected cells and stating that the DNA content of the new cells is diploid and not tetraploid. The cells purified from the adult rat heart satisfy all of the properties of cardiac stem cells. They are clonogenic, self-renewing, and able to give rise to at least three different cell types. Finally, they participate in the formation of new, functional myocardium.

Despite the convincing nature of this study, there are numerous interesting questions to be pursued. Multipotent adult progenitor cells, or MAPCs, which have also been shown to have cardiogenic potential, are characterized as being negative for the marker (c-Kit) used to define the cells in the Beltrami et al. study. In addition, the fact that the adult stem cells in this study can form endothelium, smooth muscle, and cardiac muscle is confounding, since these three cell types arise from three different cell lineages. Finally, if these cells exist and lie dormant in the heart, why do they not mobilize and divide in response to an injury? The answers to these questions will certainly make for some interesting biology and perhaps future therapies.

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Apoptosis: A Process with a (β)NAC for Complexity

Most programmed cell deaths in the nematode *C. elegans* require *ced-3* caspase activity. In a recent paper, Bloss et al. (2003) reveal a new *C. elegans* death inhibitor, *icd-1*, whose loss can promote apoptosis independently of *ced-3*.

Apoptosis (or programmed cell death), a ubiquitous metazoan cell death process, is crucial for proper organismal development, maintenance of cell number homeostasis, and elimination of diseased or otherwise harmful cells. In many instances, organismal life is impossible in the absence of the machinery for cell death. Genetic studies in model organisms have proven a fertile ground for the discovery and subsequent study of genes that regulate apoptosis. Pioneering work by Horvitz and colleagues in the 1980s identified three genes essential for